REMARKS

Rejection under 35 U.S.C. § 112, first paragraph

Claims 52-59-61, 63, 69-91 and 95 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter that was not described in the specification in such a way as to enable a person of skill in the art to make and/or use the claimed invention.

The Office bases the rejection on the allegation that "Whereas tolerance has been repeatedly induced in mice, the identical/equivalent methods have not worked in humans." OFFICE ACTION mailed 10/08/2004 at 2. In the Office Action mailed April 9, 2007, the Examiner has alleged that "it is clear, however, that the products of the claims are intended for just one use, i.e. the induction of oral tolerance to transplantation antigens." The Examiner further alleged that the invention consequently would only be applicable to humans.

The Examiner's attention is directed to page 10 of the specification and the original claims, where it is clear that applications of the methods and products of the invention include suppressing or reducing the immune response of a mammal to autoantigens involved in autoimmune disease or disorder, including lupus erythematosis, thyroiditis, multiple sclerosis, uveitis, Crohns' Disease and autoimmune diabetes, provided that the autoantigen involved in autoimmune diabetes is not glutamic acid decarboxylase. Such applications are not limited to humans. Indeed the technology has been licensed to Dow AgroSciences for applications in companion animals. (See attachment C.)

Even if the methods had never before been accomplished, the Federal Circuit has recognized that "[t]he mere fact that something has not previously been done clearly is not [] a sufficient basis for rejecting all applications purporting to disclose how to do it." *Gould v. Quigg*, 3 U.S.P.Q. 2d 1302, 1304 (Fed. Cir. 1987).

Moreover, enablement of the invention has been repeatedly demonstrated. Reports included the peer reviewed publication by Ergun-Longmire et al. (Ann. N.Y. Acad. Sci. 1029:260-277, 2004)(attachment A). The results of this study confirmed that oral administration of insulin could help patients having islet cell autoantibodies by suppressing effects of the autoimmune disease. This paper proves unequivocally that, contrary to the Examiner's contentions, it is possible to induce effective oral tolerance in humans as described in the specification and refutes any basis for alleging that the claimed methods would not work as claimed.

The attachment to the present action is just one more piece of documentary and testimonial evidence submitted by the applicants to refute the allegations made by the Office in support of the rejection. In particular, Dr. Jevnikar has submitted declarations. (Attachments to the Replies filed July 12, 2004 and February 8, 2005.) Dr. Jevnikar's declarations are supported by evidence published in peer reviewed journals that oral tolerance has been achieved in humans by Husby et al., *Journal of Immunology*, 152:4663-70, 1994 and McKown et al., *Arthritis and Rheumatism*, 43:1054-61, 2000. (Exhibits A and B attached to the Declaration of Dr. Jevnikar filed February 8, 2005) It is noted that the Ergun-Longmire et al. publication attached to this reply reports the results of a study referred to by Applicant in his declaration filed in this proceeding that, at the time of making the declaration, were not yet public.

A declaration or affidavit is, itself, evidence that must be considered. M.P.E.P. § 2164.05. When an applicant puts forth rebuttal evidence, the Office must consider it. *In re Sullivan*, 84 USPQ2d 1034, 1040 (Fed. Cir. 2007). Rebuttal evidence is "merely a showing of facts supporting the opposite conclusion." *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785

(Fed. Cir. 1984). When a patent applicant puts forth rebuttal evidence, the Office must consider that evidence. *See In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684 (Fed. Cir. 1995).

The determination of enablement should always be based on the weight of all the evidence. *Id.* "The examiner should **never** make the determination based on personal opinion." *Id.* (emphasis in original). Applicants have submitted direct *in vivo* evidence of the enablement of the method in an art accepted animal model. "[P]roof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility." *In re Brana*, 34 USPQ2d 1437, 1442 (Fed. Cir. 1995). Furthermore, evidence provided by an applicant needs to be merely convincing to one skilled in the art. M.P.E.P. § 2164.05.

The Office has relied upon a trade paper report of the cessation of a clinical trial as evidence of non-enablement. OFFICE ACTION mailed 2/10/2004, at 3 (citing *Marketletter* (1999)). The *Marketletter* is a newspaper that provides business information in order that interested persons can decide whether it is a good time to buy the stock of a particular pharmaceutical company. Applicants respectfully submit that an article about a business decision in a business journal does not provide a credible basis for rejecting the enablement of a patent application that is supported by data and evidence.

Even if the *Marketletter* were a credible source of scientific information, the article would not support the Office's allegation. The *Marketletter* article does not state that testing of Colloral was stopped not because of it was harmful or because it had no effect, but only because the statistical results did not warrant further spending on late clinical trials. The *Marketletter* is reporting a business decision, not a scientific conclusion, and not even a determination of

effectiveness by the FDA. But even an actual regulatory determination would not support the Office. The Federal Circuit has cautioned the PTO not to "confuse[] the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *In re Brana*, 34 USPQ2d 1437, 1442 (Fed. Cir. 1995).

The Office has relied upon Goodnow, *The Lancet*, 357:2115-20, 2001, but the portion of Goodnow relied upon by the Office is actually stating a conclusion regarding the action of corticosteroids. By contrast, with respect to oral tolerance Goodnow states on page 2118 that a phenomenon of oral tolerance exists and that clinical trials are underway involving the induction of oral tolerance. Goodnow does not support an allegation that oral tolerance does not work. Goodnow nether provides nor cites empirical data that convincingly refutes that oral tolerance is achievable. Rather, Goodnow supports the proposition that oral tolerance is achievable.

The Office has alleged that international application publication WO 02/053092 ("the '092 publication") teaches that "oral tolerance is fraught with numerous obstacles." In fact, the '092 publication actually demonstrates that tolerance can be accomplished and furthermore "oral and mucosal tolerance for the suppression and prevention of inflammatory conditions is well known in the art. Examples of candidate conditions, antigens and modes of therapy, can be found." WO 02/053092, at page 22, lines 25-27.

Indeed, the fact of the phenomena that underlies and enables the claimed methods is never denied in any publication cited by the Office. At most, the documents cited by the Office demonstrate that varying treatment parameters provides varying effectiveness. Experimentation to optimize treatment parameters is not necessarily undue if the art typically engages in such experimentation. *See, e.g., In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ

1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985); s*ee also In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976); M.P.E.P. § 2164.01.

In view of all the evidence submitted (including the Declarations of Dr. Jevnikar), and the absence of credible proof of non-enablement, there is no reason to doubt that one skilled in the art could make and/or use the claimed invention without undue experimentation. The rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 52, 59-61, 63, 69-91 and 95 have been rejected under 35 U.S.C. § 103 as allegedly unpatentable over PCT published application WO 92/07581 in view of U.S. Patent No. 5,484,719 ("the '719 patent").

The prior art fails to establish a proper prima facie case of obviousness. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143.

The cited art fails to teach every element of the claimed invention. WO 92/07581 teaches a method for suppressing an immune response by administering cell extracts from donor tissue.

Nowhere in the WO 92/07581 publication is it suggested that oral administration of a transgenic plant is an alternative method of suppressing an immune response. The '719 patent does not cure the deficiencies of WO 92/07581, because the '719 patent also fails to disclose oral administration of plants for suppression of an immune response.

One skilled in the art would not be motivated to combine and modify these two references, because the objectives of the two references are diametrically opposed and combining the references as proposed would change the principle of operation of the '719 patent. The objective of the '719 patent is the opposite of the objective of the present application. The '719 patent teaches that expression of antigens from viral, bacterial or fungal antigens in a plant for a method of oral vaccination will have the effect of increasing the immune response. The present application is directed to the induction of oral tolerance with tolerogenic antigens with the object of suppressing an immune response.

If oral ingestion were to induce tolerance to the viral, bacterial or fungal antigens of the '719 patent, it would be the opposite of the desired effect. If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 U.S.P.Q. 1125 (Fed. Cir. 1984). If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 U.S.P.Q. 349 (CCPA 1959).

The combination of references fails to teach every element of the claimed invention. Moreover, as a matter of law, there would have been no motivation to modify and combine the

cited references. For at least these reasons, the proposed combination fails to support a *prima facie* case of obviousness.

Furthermore, secondary indicia of non-obviousness also exist. For example, Dr. Jevnikar has been recognized in the art for his novel contributions in the field of immune research by the Kidney Foundation of Canada (See attachment B). The report of the award specifically refers to Dr. Jevnikar's "Novel expression and drug delivery systems for topical and oral delivery of proteins that modulate the body's immune response." The technology addresses a long felt but unmet need such that the technology described and claimed in this that has been recognized for commercial development in the field Under a licensing agreement, Dow AgroSciences Canada, Inc. is developing the technology for use with companion animals. (See attachment C).

For at least these reasons, withdrawal of the rejection is appropriate.

Obviousness-type double patenting rejection

Claims 52, 59-61, 63, 69-91 and 95 have been rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-17 of U.S. Patent Number 6,338,850. Without acceding to the alleged basis of the rejection, applicants have filed herewith a terminal disclaimer so as to render the matter moot.

Claims 63, 69-71, 78-83 and 88-95 have been provisionally rejected over claims 11-16 of U.S. Patent Application 10/137,647. The rejection is provisional, applicants will address the merits of the rejection if it becomes non-provisional.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

The Director is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: October 9, 2007

By: /Christopher L. North/
Registration No. 50433

P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620